phosphate and glucosamine using capillary electrophoresis. Therefore, the Examiner contends that it would have been obvious to make glucosamine according to Claims 1-6, 8, 14-16, 18 and 21 since the rationale, reagents and process steps are allegedly known. The Examiner asserts that glucosamine is expected to be produced by the method of Dutka-Malen et al., and that the products are expected to be recovered using the method of O'Shea et al. The Examiner contends that a further step of dephosphorylating glucosamine-6-phosphate is expected to be obtained because phosphatases are commercially available. The Examiner submits that because methods are well known to increase the cell density of *E. coli* in culture such as culturing in TB, glucosamine is expected to be produced at concentrations of at least 1 g/L and the products recovered using the methods of O'Shea. Finally, the Examiner asserts that one of ordinary skill in the art would be motivated to produce glucosamine by the methods of Claims 1-6, 8, 14-16, 18 and 21 because of the need for new cost-effective methods for production of glucosamine. The Examiner asserts that there is a reasonable expectation of success because the reagents and process steps for production of glucosamine according to Claims 1-6, 8, 14-16, 18 and 21 are known in the art and because Dutka-Malen et al. had success in producing a genetically modified microorganism which overexpresses glucosamine-6 phosphate synthase.

Applicants traverse the rejection of Claims 1-6, 8, 14-16, 18 and 21 under 35 U.S.C. § 103(a), and submit that these claims are not obvious over the combination of Dutka-Malen et al. and O'Shea. Initially, Applicants note that for a *prima facie* case of obviousness to be established, the following three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Third, the combination of references must teach or suggest all of the claim limitations.

Applicants submit that the combination of references does not meet all of the above-requirements for a case of *prima facie* obviousness. First, Applicants submit that the combination of references does not teach or suggest all of the claim limitations. Specifically, Applicants submit that Dutka-Malen et al. do not teach that a step of culturing produces a product selected from the group consisting of glucosamine-6-phosphate and glucosamine. Applicants submit that Dutka-Malen et al. only teach a molecule encoding the wild-type

glucosamine-6-phosphate synthase; Dutka-Malen et al. *do not measure any glucosamine* produced by the microorganism, and *do not provide any evidence* that the expression of their recombinant nucleic acid molecule increases production of glucosamine by the microorganism. Therefore, there is no teaching of a production of glucosamine or glucosamine-6-phosphate by Dutka-Malen et al. Moreover, as the Examiner has admitted, Dutka-Malen et al. do not teach a method for isolating glucosamine-6-phosphate or glucosamine. As discussed above, Applicants additionally note that Dutka-Malen et al. do not teach or suggest even attempting to *detect* whether the *E. coli* actually produce glucosamine-6-phosphate or glucosamine, let alone the recovery of glucosamine-6-phosphate or glucosamine. Therefore, Dutka-Malen et al. fail to teach each and every element of the claimed invention.

Applicants submit that the reference of O'Shea does not make up for the deficiencies of Dutka-Malen et al. More particularly, O'Shea is a technical reference which describes *analytical* methods for *detecting* carbohydrates, such as the detection of glucose in blood. As such, the method is used for, and indeed is promoted for, "its ability to analyze extremely small volumes" (See Introduction, second paragraph). O'Shea et al. does not teach or suggest a method for recovery of carbohydrates, including glucosamine, such as from a culture medium or a microorganism. In summary, O'Shea does not teach the genetic modification of a microorganism, the culturing of a microorganism, nor any step of producing or recovering glucosamine or glucosamine-6-phosphate from a microorganism or fermentation medium.

In summary, Applicants submit that the combination of references does not teach or suggest every element of claims. Specifically, neither Dutka-Malen et al. nor O'Shea et al., alone or in combination, teach or suggest a method to produce glucosamine by fermentation, which includes the steps of: culturing a microorganism that has a genetic modification to increase the action of glucosamine-6-phosphate synthase, such that glucosamine or glucosamine-6-phosphate is produced; and, recovering the product. It is well established that for a rejection under § 103 to be proper, all the claim limitations must be **taught or suggested** by the prior art. *In re Royka*, 180 USPQ 580 (CCPA, 1970).

With regard to the requirement that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings, Applicants provide the following

rebuttal of the Examiner's position. First, it is noted that Dutka-Malen et al. do not provide any *motivation* to recover glucosamine-6-phosphate or glucosamine from the fermentation medium or from the microorganism. Indeed, the reference of Dutka-Malen et al. is directed to the cloning of the *glmS* gene and the investigation of the catalytic properties of the enzyme through *in vitro* methodology (See page 288, col. 1, second full paragraph). Second, Applicants submit that there is no motivation provided in O'Shea et al. to use their analytical method for recovery of a carbohydrate produced in a fermentation process, since the method of O'Shea is specifically designed to detect and analyze compounds present in small volumes and/or compounds which are difficult to detect, and *not* to recover compounds, including carbohydrates or specifically glucosamine, from a culture medium.

Third, Applicants submit that the Examiner's contention that one of ordinary skill in the art would be motivated to produce glucosamine-6-phosphate and glucosamine because of the need for new cost-effective methods for production of glucosamine is not a sufficient basis to reject the present claims on the basis of obviousness. More specifically, stating a "need in the art" does not tell one of skill in the art how to meet that need, or more particularly, which references should be pulled together to attempt to address that need. Applicants submit that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggesting supporting the combination. ACS Hospital Systems v. Montofiore Hospital, 221 USPQ 929, 933 (Fed.Cir. 1974). As will be recognized, claims cannot be found obvious unless the prior art **teaches or suggests** making the claimed product or process. *See In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir., 1991) (The teaching or suggestion to make the claimed combination or modification and the reasonable expectation of success must **both be found** in the prior art), *In re Mills*, 16 USPQ2d 1430 (Fed. Cir., 1990) (The mere fact that references can be combined or modified does **not** render the resultant combination or modification obvious **unless** the prior art also **suggests the desirability** of the combination or modification. Thus, although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there **must be a suggestion or motivation in the reference** to do so").

Applicants respectfully submit that the Examiner has failed to provide any evidence of a teaching or motivation to modify the combination of references to arrive at the present invention. Applicants submit that the Dutka-Malen et al. and O'Shea et al. references are devoid of any suggestion of a method to produce glucosamine-6-phosphate or glucosamine by fermentation and/or to recover such products from a fermentation medium. It appears that in the present case the only suggestion for the Examiner's combination of the teachings in Dutka-Malen et al. and O'Shea et al. improperly stems from the Applicants' own disclosure and not from the cited references themselves. At best, the Examiner's comments regarding inventive step appear to amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at Applicants' invention because they would have had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. "A statement that modifications of the prior art to meet the claim limitations would have been 'well within the ordinary skill of the art at the time the invention was made', because the cited references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)." MPEP 2143.01. Applicants submit that neither of the references, alone or in combination, provide an impetus necessary to cause one skilled in the art to combine the teachings of the references in the way the Examiner has done.

With regard to the Examiner's contention that one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to recover intracellular or extracellular glucosamine-6-phosphate, to dephosphorylate the glucosamine-6-phosphate, or to produce at least 1 g/L of product because various recovery methods, dephosphorylation methods and culture methods are "known", is similarly not a proper standard for obviousness. Again, because one of skill in the art would have had the necessary skills to perform a method with an expectation of success, does not provide motivation to actually conceive of any or all of the steps of a process, or of the process as a whole. The Examiner has not pointed to any teaching or suggestion in any of the cited references to look for intracellular or secreted glucosamine, to dephosphorylate glucosamine-6-phosphate, or to produce any amount of glucosamine by fermentation, including at least 1 g/L. There is no teaching or suggestion whereby a person of

ordinary skill would have been led to select the various steps of the present method and combine them as the Examiner has done. To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction -- an illogical and inappropriate process by which to determine patentability. W.L. Gore & Assoc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983). The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985). The Examiner has provided no basis in the art for producing and recovering glucosamine or glucosamine-6-phosphate by a fermentation method. To merely state that glucosamine was a desirable commercial product at the time of the present invention is not sufficient evidence that one of ordinary skill in the art would have found the present method obvious.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-6, 8, 14-16, 18 and 21 under 35 U.S.C. § 103(a).

2.0 Rejection of Claims 7 and 17 Under 35 U.S.C. § 103(a):

The Examiner has rejected Claims 7 and 17 under 35 U.S.C. § 103(a), contending that these claims are unpatentable over Plumbridge in view of Joyce et al. and O'Shea et al. Specifically, the Examiner contends that Plumbridge teach the *E. coli* genes: *nagA, nagB, nagC, nagD, nagE,* and *manXYZ.* The Examiner admits that Plumbridge do not teach a genetic modification wherein the modification is a mutation in an *E. coli* gene according to Claims 7 and 17. The Examiner asserts that Joyce et al. teach a method to delete specific genes from the *E. coli* genome and the successful use of the method to delete the *polA* gene from the *E. coli* genome. Therefore, the Examiner contends that it would have been obvious to make an *E. coli* cell having a mutation according to Claims 7 and 17 for use in the method of Claim 1 by deleting any one of the genes taught by Plumbridge using the method taught by Joyce et al. The reference of O'Shea is cited for the teachings asserted in the first rejection under § 103 discussed above. The Examiner again asserts that motivation is provided by the need for new cost-effective methods for production of glucosamine.

Applicants traverse the Examiner's rejection of Claims 7 and 17 under 35 U.S.C. § 103(a). First, Applicants note that Claims 7 and 17 depend from Claim 1, the rejection of which has been traversed above. Therefore, in view of the above-remarks alone, Applicants submit that these claims are not obvious in view of the cited combination of references. With particular regard to the combination of Plumbridge et al., O'Shea et al. and Joyce et al., Applicants submit that the teaching of Plumbridge of the description of several *E. coli* genes is completely insufficient to establish a case of obviousness, even in combination with the references of Joyce et al. and O'Shea et al. As the Examiner admits, Plumbridge does not teach or suggest modifying any of the genes recited in Claims 7 or 17, and in particular, Plumbridge does not teach or suggest modifying any genes for the purpose of increasing glucosamine production by a microorganism.

The deficiencies of O'Shea et al. are discussed above in Section 1.0 with regard to the rejection of Claims 1-6, 8, 14-16, 18 and 21, and equally apply to Claims 7 and 17.

With regard to Joyce et al., the Examiner appears to contend that the teachings of Joyce et al., which are directed to the modification of the gene encoding DNA polymerase I (*polA*), somehow provides a teaching or suggestion to make one or more of the modifications recited in Claims 7 and 17. Applicants submit that Joyce et al. does not teach any one of the modifications recited in Claims 7 or 17 and does not provide any suggestion or motivation to turn from the study of DNA polymerase I to a gene involved in the amino sugar metabolic pathway. At best, Joyce et al. demonstrate a method of determining whether an *E. coli* gene is essential for viability, and that *polA* is required for growth of *E. coli* on rich medium but not minimal medium. Such teachings do not make up for the deficiencies of Plumbridge et al. and O'Shea et al. and indeed, the present claims are not directed to a method for generating mutations in an organism but rather, for using specific mutations that result in enhanced glucosamine production.

In summary, Applicants submit that none of the cited references, alone or in combination, teach or suggest to one of ordinary skill in the art to modify the pathways recited in the claims. Additionally, Applicants submit that the Examiner has failed to point to any portion of Plumbridge, Joyce et al. or O'Shea et al. which would suggest to one of skill in the art to modify any of the genes recited in Claims 7 or 17 for the purpose of increasing glucosamine production by a microorganism and therefore, there is no motivation in the cited references to

make the combination as the Examiner has done. Moreover, Applicants again refer to the argument in Section 1.0 above in traverse of the Examiner's contention that the motivation lies in a "need in the art for new cost-effective methods for production of glucosamine".

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 7 and 17 under 35 U.S.C. § 103.

3.0 Rejection of Claim 9 Under 35 U.S.C. § 103(a):

The Examiner has rejected Claim 9 under 35 U.S.C. § 103, contending that this claim is unpatentable over Dutka-Malen et al. in view of Balbas et al. and O'Shea et al. Specifically, the Examiner reiterates the asserted teachings of Dutka-Malen et al. and O'Shea et al. The Examiner admits that Dutka-Malen et al. do not teach methods for producing glucosamine-6-phosphate wherein the gene encoding glucosamine synthase is integrated into the *E. coli* genome. The Examiner contends that Balbas et al. teach a vector for chromosomal integration of cloned DNA into the *E. coli* genome and the successful integration of the *Vitreoscilla* sp. hemoglobin-encoding gene and the *Photobacterium leiognathi lux* genes into the *E. coli* genome. Therefore, the Examiner contends that it would be obvious to produce glucosamine according to Claim 9 because the rationale, reagents and process steps are known. The Examiner asserts that one would be motivated to clone the gene into *E. coli* using the integrative vector of Balbas et al. because of advantages taught by Balbas et al.

Applicants traverse the rejection of Claim 9 under 35 U.S.C. § 103. Initially, Applicants again refer to the arguments presented in traverse of the combination of Dutka-Malen et al. and O'Shea et al. in Section 1.0 and submit that these references fail to teach or suggest the present invention or provide the requisite motivation to make and use the invention. Since Claim 9 depends from Claim 1, these arguments apply to Claim 9.

Applicants additionally submit that the teachings of Balbas et al. regarding the integration of *completely unrelated genes* into *E. coli* do not make up for the deficiencies of either of Dutka-Malen et al. or O'Shea et al. Balbas et al. are not concerned with the production of glucosamine or glucosamine-6- phosphate and therefore, can not provide any teaching or motivation to make the combination with the other references. In brief, the Examiner has failed to point to any teaching in any of the cited references which teaches or suggests the claimed

method, including that the glucosamine-6-phosphate synthase gene be integrated into the genome of a microorganism. Again, it appears that the only suggestion for the Examiner's combination of the teachings in Dutka-Malen et al., Balbas et al. and O'Shea et al. improperly stems from the Applicants' own disclosure and not from the cited references themselves.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claim 9 under 35 U.S.C. § 103.

4.0 Rejection of Claims 10 and 19 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 10 and 19 under 35 U.S.C. § 103, contending that these claims are unpatentable over Dutka-Malen et al. in view of O'Shea et al. Specifically, the Examiner reiterates the general rejection as presented in Section 1.0 above and further contends that glucosamine or glucosamine-6-phosphate is expected to be produced according to Claims 10 and 19 by modifying the teachings of Dutka-Malen et al. in which the DNA encoding the synthase gene is mutated by site-directed mutagenesis, UV irradiation or treatment with a mutagenic agent and selecting host cells which contain a glucosamine synthase with reduced product inhibition. The Examiner contends that it would have been obvious to do these steps based on the motivation as discussed in Section 1.0 above.

Applicants traverse the Examiner's rejection of Claims 10 and 19 under 35 U.S.C. § 103. Applicants again refer to the arguments presented in traverse of the combination of Dutka-Malen et al. and O'Shea et al. in Section 1.0 and submit that these references fail to teach or suggest the present invention or provide the requisite motivation to make and use the invention. Since Claims 10 and 19 depend from Claims 1 and 18, respectively, these arguments apply equally to Claims 10 and 19. Moreover, the Examiner has failed to point to any teaching in either of the cited references, or in the art in general, which teaches or suggests that the glucosamine-6-phosphate synthase gene should be mutated to reduce *N*-glucosamine-6-phosphate product inhibition of the synthase. Again, Applicants submit that the Examiner has relied on a generalized "need" in the art and the availability of well known methods, without pointing to any specific teaching which provides the requisite motivation to modify the cited references as the Examiner has done. It appears that the only suggestion for the Examiner's combination of the

teachings in Dutka-Malen et al. and O'Shea et al. improperly stems from the Applicants' own disclosure and not from the cited references themselves.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 10 and 19 under 35 U.S.C. § 103.

5.0 Rejection of Claims 11-13 and 20 Under 35 U.S.C. § 103(a):

The Examiner has rejected Claims 11-13 and 20 under 35 U.S.C. § 103, contending that these claims are unpatentable over Dutka-Malen et al. in view of Plumbridge, Joyce et al. and O'Shea et al. Specifically, the Examiner adds to the discussion of these references as set forth in the sections above by asserting that it would have been obvious to make a microorganism according to Claims 11-13 and 20 for use in the method of Claims 1 or 18 since the rationale, reagents and process steps for making the microorganism were known. The motivation for deleting any gene or genes as taught by Plumbridge using the method of Joyce et al. for production of a microorganism useful in the method for production of glucosamine is said to be provided by the need for new cost-effective methods for production of glucosamine.

Applicants traverse the Examiner's rejection of Claims 11-13 and 20 under 35 U.S.C. § 103. Again, Applicants refer to the arguments presented in traverse of the combination of Dutka-Malen et al. and O'Shea et al. in Section 1.0 and submit that these references fail to teach or suggest the present invention or provide the requisite motivation to make and use the invention. Since Claims 11-13 and 20 depend from Claims 1 and 18, respectively, these arguments apply equally to Claims 11-13 and 20. Moreover, Applicants refer to the arguments presented against the references of Plumbridge et al. and Joyce et al. in Section 2.0 and again submit that the Examiner has failed to point to any portion of Plumbridge or Joyce et al. which would suggest to one of skill in the art to modify any of the genes recited in Claims 11-13 or 20 for the purpose of increasing glucosamine production by a microorganism. The Examiner's basis for motivation has been traversed in the sections above and such arguments are incorporated under this section. Again, it appears that the only suggestion for the Examiner's combination of the teachings in Dutka-Malen et al., O'Shea et al., Plumbridge and Joyce et al. improperly stems from the Applicants' own disclosure and not from the cited references themselves.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 11-13 and 20 under 35 U.S.C. § 103.

6.0 Rejection of Claims 22, 23, 27-29 and 33 Under 35 U.S.C. § 103(a):

The Examiner has rejected Claims 22, 23, 27-29 and 33 under 35 U.S.C. § 103, contending that these claims are unpatentable over Dutka-Malen et al. in view of Balbas et al. and O'Shea et al. The Examiner again refers to the arguments presented with regard to Dutka-Malen et al. and Balbas et al. as set forth in sections above. The Examiner admits that Dutka-Malen et al. do not teach a microorganism according to Claims 22, 23, 27-29 and 33, but submits that it would have been obvious to make such a microorganism since the rationale, reagents and process steps were allegedly known. The Examiner asserts that the microorganism is expected to be produced by modifying the teachings of Dutka-Malen et al. by a mutation technique and the mutated DNA inserted into the integrative vector of Balbas et al. The Examiner again states that methods were known to increase the cell density of *E. coli* in culture and that one of skill in the art would be motivated to produce the microorganism because of the need for new cost-effective methods for production of glucosamine.

Applicants traverse the Examiner's rejection of Claims 22, 23, 27-29 and 33 under 35 U.S.C. § 103. The arguments against Dutka-Malen et al., O'Shea et al. and Balbas et al. as presented above are again referenced and incorporated here. Specifically, Applicants submit that the Dutka-Malen et al. and O'Shea et al., alone or in combination with Balbas et al., do not teach or suggest the method of the present invention, and therefore, there can not be any motivation provided by these references to make a microorganism useful in such a method. For the purposes of discussion, it is noted that Claim 22 recites a microorganism that is transformed with a recombinant nucleic acid molecule encoding *N*-glucosamine-6-phosphate synthase, wherein the recombinant nucleic acid molecule is operatively linked to a transcription control sequence and comprises a genetic modification which reduces *N*-glucosamine-6-phosphate product inhibition of *N*-glucosamine-6-phosphate synthase. Applicants submit that the Examiner has failed to provide any teaching or suggestion in Dutka-Malen et al., O'Shea et al. or Balbas et al., or indeed, in the art, for making any modification to the glucosamine-6-phosphate synthase gene, including the specific modifications described in Claim 22 (and thus dependents therefrom).

Therefore, the combination of references fails to teach each and every element of the claims. More particularly, with regard to independent Claim 22, the Examiner has not provided any teaching or suggestion in the art to modify the synthase gene to reduce glucosamine-6-phosphate product inhibition, nor even a teaching that such product inhibition *occurs*, and in fact, the Examiner has not provided any teaching or suggestion in the art to make any modifications to the synthase gene at all. Furthermore, it is was not obvious until the present invention that it would even be *possible* to isolate a feedback resistant variant of the enzyme.

Again, Applicants submit that the Examiner has relied on a generalized "need" in the art and the availability of well known methods, without pointing to any specific teaching which provides the requisite motivation to modify the cited references as the Examiner has done. Indeed, Applicants submit that the Examiner's case for obviousness can only become apparent after review of Applicants' specification, where it is first demonstrated that the isolation of mutant microorganisms and/or derivative sequences of the synthase gene as claimed in Claim 22 leads to greatly increased glucosamine production. Therefore, Applicants submit that the Examiner has improperly used hindsight reconstruction to make a case of obviousness.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 22, 23, 27-29 and 33 under 35 U.S.C. § 103.

7.0 Rejection of Claims 24-26 and 30-32 Under 35 U.S.C. § 103(a):

The Examiner has rejected Claims 24-26 and 30-32 under 35 U.S.C. § 103, contending that these claims are unpatentable over Dutka-Malen et al. in view of Balbas et al., Plumbridge and Joyce et al. The Examiner refers to the arguments with regard to each of these references as set forth under previous rejections and admits that Dutka-Malen et al. do not teach a microorganism according to Claims 24-26 and 30-32. The Examiner asserts, however, that it would have been obvious to make a microorganism according to these claims since the rationale, reagents and process steps were allegedly known. The Examiner states that the microorganism according to Claims 24-26 and 30-32 is expected to be produced by further modifying the microorganism as described in Section 6.0 above in which any gene taught by Plumbridge is deleted using the method of Joyce et al. Again, the Examiner points to an alleged need for new cost-effective methods for production of glucosamine as motivation to make such modifications.

Applicants traverse the Examiner's rejection of Claims 24-26 and 30-32 under 35 U.S.C. § 103. Initially, the arguments presented above against the rejection of Claims 22, 23, 27-29 and 33 are referenced and again asserted. Since Claims 24-26 and 30-32 depend from Claim 22, those arguments apply equally to these claims. Moreover, as discussed in other sections above, Applicants submit that Plumbridge does not teach or suggest modifying any of the genes recited in Claims 24-26 and 30-32, and at best, Joyce et al. demonstrate a method of determining whether an *E. coli* gene is essential for viability, and that *polA* is required for growth of *E. coli* on rich medium but not minimal medium. Finally, the teachings of Balbas et al. regarding the integration of *completely unrelated genes* into *E. coli* do not make up for the deficiencies of the combination of Dutka-Malen et al., Plumbridge and Joyce et al. Therefore, Applicants submit that none of the cited references, alone or in combination, teach or suggest to one of ordinary skill in the art to modify the pathways to produce the microorganism recited in the claims. Additionally, Applicants submit that the Examiner has failed to point to any portion of any of the cited references which would suggest to one of skill in the art to modify any of the genes recited in Claims 24-26 and 30-32 for the purpose of increasing glucosamine production by a microorganism and therefore, there is no motivation in the cited references to make the combination as the Examiner has done. Finally, Applicants again refer to the arguments above in traverse of the Examiner's contention that the motivation lies in a "need in the art for new cost-effective methods for production of glucosamine" and submit that this is an inappropriate standard for obviousness.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 24-26 and 30-32 under 35 U.S.C. § 103.

8.0 Rejection of Claims 34-39 Under 35 U.S.C. § 103(a):

The Examiner has rejected Claims 34-39 under 35 U.S.C. § 103, contending that these claims are obvious over Dutka-Malen et al. in view of Balbas et al., Plumbridge, Joyce et al. and O'Shea et al. The Examiner refers to the previous discussion of these references as set forth under rejections above, and admits that Dutka-Malen et al. do not teach the microorganism according to Claims 34-39. The Examiner contends, however, that it would have been obvious to make such a microorganism because the rationale, reagents and process steps were allegedly

known. The Examiner asserts that a microorganism is expected to be produced according to Claims 34-39 by inserting the synthase gene of Dutka-Malen et al. into an integrative vector as taught by Balbas et al., transforming *E. coli* hosts, selecting cells with an increased expression of enzyme activity, and any gene as taught by Plumbridge is deleted using the method of Joyce et al. The Examiner contends that the motivation to combine these references is found in the need for a new cost-effective method for production of glucosamine.

Applicants traverse the Examiner's rejection of Claims 34-39 under 35 U.S.C. § 103. The arguments against Dutka-Malen et al., O'Shea et al., Balbas et al., Plumbridge, and Joyce et al., as presented above, are again referenced and incorporated here. Specifically, Applicants submit that none of Dutka-Malen et al., O'Shea et al., Balbas et al., Plumbridge or Joyce et al., alone or in combination, teach or suggest the microorganism as claimed in Claims 34-39. For the purposes of discussion, it is noted that Claim 34 recites a microorganism that: (1) is transformed with a recombinant nucleic acid molecule encoding *N*-glucosamine-6-phosphate synthase, wherein expression of said *N*-glucosamine-6-phosphate synthase by the microorganism is increased; and, (2) has at least one genetic modification in a gene encoding a protein involved in an amino sugar metabolic pathway. Applicants submit that the Examiner has failed to provide any teaching or suggestion in any of the cited references or in the art in general to modify the pathways to produce the microorganism recited in the claims. Additionally, Applicants submit that the Examiner has failed to point to any portion of any of the cited references which would suggest to one of skill in the art to modify any of the genes recited in Claims 34-39 for the purpose of increasing glucosamine production by a microorganism and therefore, there is no motivation in the cited references to make the combination as the Examiner has done. Finally, Applicants again submit that the Examiner's case for obviousness can only become apparent after review of Applicants' specification, where it is first demonstrated that the isolation of mutant microorganisms as claimed in Claims 34-39 leads to greatly increased glucosamine production. Therefore, Applicants submit that the Examiner has improperly used hindsight reconstruction to make a case of obviousness.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 34-39 under 35 U.S.C. § 103.

Applicants have attempted to respond to all of the Examiner's concerns as raised in the July 20 Office Action. In the event that the Examiner has any questions regarding Applicants' position, the Examiner is invited to contact the below-named agent at (303) 863-9700.

Respectfully submitted,

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